General Principles

Introduction to General Pharmacology (Gen Pharm)

This series of lessons covers the mundane portions of pharmacology—how the drug gets in, through, and out of the body (**pharmacokinetics**)—then discusses interactions at the molecular level—how drugs actually do what they do to receptors (**pharmacodynamics**)—finishing off with clinical applications in the autonomic nervous system. If you have done this course in the order we intend (Biochemistry module first, General Physiology before General Pharmacology), you'll see some redundancy. That redundancy is intentional as we look at concepts from physiology and biochemistry but from a pharmaceutical and clinical perspective.

The Flow of the General Pharmacology Course

Pharmacokinetics is broken down into **absorption** (from air to plasma), **distribution** (from plasma to tissues), **metabolism** (breakdown in tissues), and **elimination** (from plasma to toilet), covered in lessons 2 through 5. Each lesson introduces concepts that are used in subsequent lessons. These concepts are slow going for a lot of people because the specifics don't come intuitively, which is why we've broken them up over five lessons. Ours are shorter than most, with fewer images to grapple with; we hope to solidify these concepts to ensure that the rest of pharmacology becomes simpler. The goal is not complete truth from a pharmacology textbook, but rather sufficient understanding to engage clinical pharmacology.

We then go into **pharmacodynamics** in lesson 6, revisiting biochemistry in clinical fashion, looking at antagonists and agonists at the receptor level—efficacy, potency, and affinity. We round off pharmacodynamics with the physiology of receptors in lesson 7, reviewing ionotropic and metabotropic receptor systems from physiology now from the perspective of clinical application—using receptors to treat disorders of the autonomic nervous system.

We finish General Pharmacology with the **autonomic nervous system** in lessons 8 through 10. This system is often the subject of board examinations because it gives test-takers opportunities for deductive reasoning. If the system is well understood, memorization isn't necessary. Other courses dwell on the autonomic system; we don't. You will learn the anatomy and physiology of the parasympathetic and sympathetic nervous systems. You will engage drug names, side effects, and mechanisms of action, but it will be in the context of the receptor physiology. We then reserve the specifics of medication indications for the organ system they are used to treat—β_1 blockers in coronary artery disease (Cardiac), β_2 agonists in COPD (Pulmonology). The goal is to get the molecular physiology of the receptors down, then really engage medications later, where they belong tagged to the diseases they treat.

General Principles of Kinetics = Diffusion

Everything you learn here will be used in the rest of pharmacokinetics. Diffusion is everything. And although medications do follow the laws of diffusion, practical application of the diffusion equation to drugs is not the same as the diffusion equation in a chemistry experiment. We start with the diffusion equation as it appears in chemistry to orient the variables, then show you the pharmacokinetic parallels as the equation is applied to real people.

Diffusion of a molecule is the movement of the molecule across a membrane. The diffusion of a molecule is proportional to the **solubility** of the drug (*K*), the **concentration gradient** ([gradient]) across the membrane, and the **surface area** (SA) of the membrane across which it diffuses. The diffusion of a molecule is inversely proportional to the **thickness** of the membrane (how far the molecule must diffuse) and the **size** of the molecule (smaller molecules diffuse more easily).

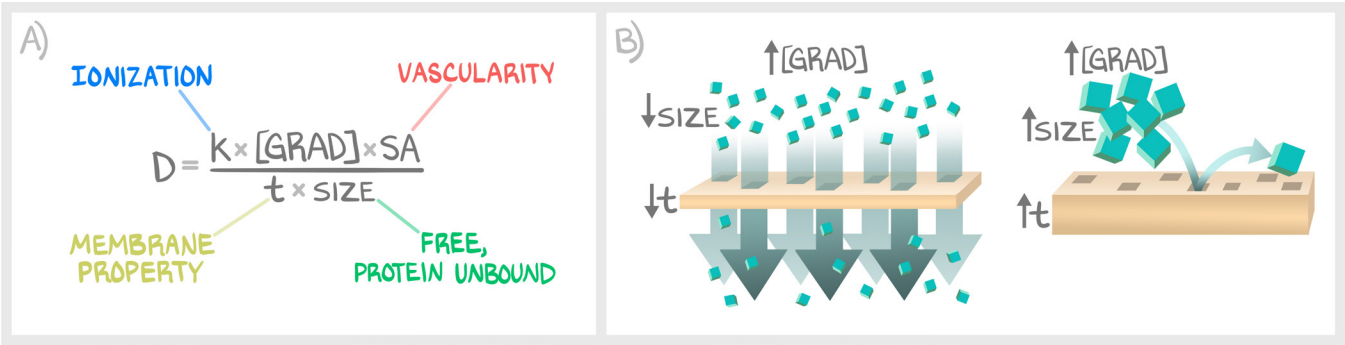

Figure 1.1: The Diffusion Equation
(a) The regular diffusion equation is in grey with the general pharmacology correlates layered on top. (b) Varying the classic principles of diffusion, showing thin membranes and small molecules readily diffuse, large ones don't.

When it comes to the pharmacokinetics of a drug in the human body, things are not so simple. The key here is threefold. First, the "membrane" the drug must diffuse across is the cell's plasma membrane. Second, almost every drug we administer is too large to diffuse across the plasma membrane. Third, there are many compartments in the human body—the gut, the bloodstream, the target organ—and each compartment is separated by a plasma membrane. So we now correlate the concepts of the diffusion equation to how pharmacology works.

The **concentration gradient** works the same way in general chemistry as it does in pharmacology and in clinical practice. The more of a drug that is in one compartment, the stronger the diffusion force for that drug to go into a compartment with less drug. If there were a semipermeable membrane (like those explanations in undergraduate chemistry), drugs would easily diffuse from one compartment to another. The difference in pharmacology is that there isn't a semipermeable membrane—there is a very impermeable lipid bilayer of every plasma membrane of every cell. Because compartments are separated by cells with impermeable membranes, the concentration gradient isn't what restricts or allows movement of drugs between compartments. The concentration gradient is the driving force, but solubility (discussed below) is the main feature of a drug that lets it move between compartments.

The **surface area** is less the physical surface area of a plasma membrane on one cell, and more the **vascularity** of an organ. When a person inhales a medication, the surface area of the alveoli does matter. For every other organ, you should identify the surface area of the diffusion equation with vascularity. More drug is delivered to an organ that has more blood flow. Decreased perfusion or an obstructed artery denies delivery of the drug.

Size of the drug, we already learned, is irrelevant—every drug is too big simply to diffuse through the plasma membrane. But there are specialized endothelial layers that are looser than others, so that some drugs can simply leave the bloodstream into the target organ. But albumin, a protein in plasma, is far too large to exit the bloodstream. Therefore, instead of referring to size, we are going to refer instead to the free fraction, how much of the drug is in a **protein-bound state**. Drugs that bind to albumin cannot leave the bloodstream, just as albumin cannot leave the bloodstream. This becomes more relevant when the drug is already in the body, so we discuss it under distribution and elimination. The only meaningful exception to "all drugs are too large to diffuse" is oxygen, which is so small it diffuses through plasma membranes. You should learn that every other drug is too large to fit through a plasma membrane, so must go between them, and then, only if free from albumin.

The **thickness** of the membrane has some clinical applications. For the most part, the linings of capillaries, the endothelial cells, are about the same thickness, so thickness "doesn't matter." Plasma membranes of cells are a fixed thickness, so thickness "doesn't matter." But where thickness does play a role is in the route of administration and in pathologic states. For example, an intravenous dose is injected into the vein directly, and a subcutaneous dose is injected into the subcutaneous fat. The distance the drug must diffuse in the intravenous dose is 0, whereas the distance the subcutaneous dose must travel is larger: through the fat and into vasculature. The other example is in pulmonary edema—if there is a column of water interrupting the diffusion of oxygen, less oxygen will end up in the capillaries.

We finish with solubility because it is the most complex, and likely the most important. We said the plasma membrane was impermeable to drugs. That is only partially true. **Lipophilic** drugs are able to diffuse through the plasma membrane. The more lipid soluble a drug is, the more easily it diffuses through membranes.

Solubility means whether a drug is **water soluble (trapped in the compartment it's in)** or **lipid soluble (can move through cell membranes)**. Polarity does influence hydrophilic vs. hydrophobic, but in pharmacology solubility is discussed in relation to **ionization**. Ionized means hydrophilic, and being trapped in the compartment. Un-ionized means lipophilic and diffusing through plasma membranes. Ionization forces us to go back to biochemistry, back to talking about p*K*s and pH.

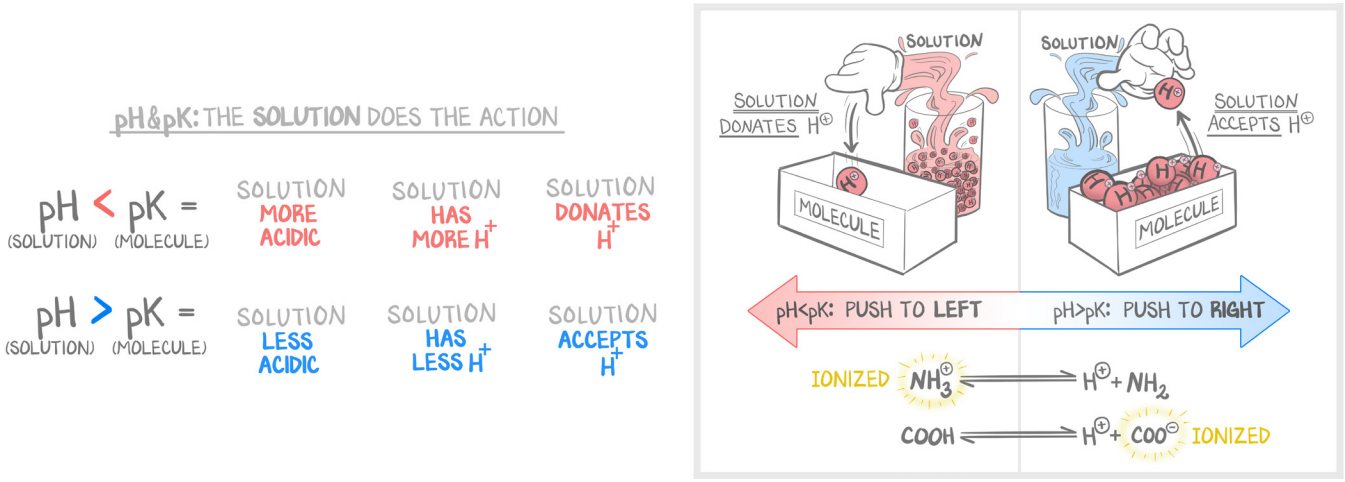

Figure 1.2: pH and pK
The key to deducing the effect of pH is to assess the system from the perspective of the solution, asking whether the solution has more H^+ than the molecule (i.e., it will donate to the molecule) or less H^+ than the molecule (it will steal from the molecule). The solution's H^+ is measured by the pH, and the drug's H^+ is measured by the pK. Just be careful—the lower the pH, the more H^+ ions the solution has.

pH is **of the medium**; it can change. The **p*K*** is **of the drug**; it cannot change. If a solution has a lower pH than the p*K* of the drug, the solution is more acidic, the solution has more H^+ ions than the drug, and **the solution will donate H^+ to the drug**. If a solution has a higher pH than the p*K* of the drug, the solution is less acidic than the drug, the solution has fewer H^+ ions, and **the solution will take H^+ from the drug**.

p*K* is of the drug; the drug has one p*K* value. A drug can be a **weak acid** or a **weak base**. This is easiest to understand if we simplify it with examples. We use a similar explanation to the one we used in Biochemistry, when discussing amino acids. There, we defined the carboxyl group (COOH) as the weak acid and the amine group (NH_3^+) as the weak base. Atlhough a drug's molecular makeup involves far more groups, dividing all drugs into Drug-COOH and Drug-NH_3^+ helps keep this explanation from getting unwieldy.

Start with this: "An **acid** will exist **un-ionized in acidic environments**, whereas a **base** will exist **un-ionized in basic environments**." Or said differently, remember "un-ionized in like environments: un-ionized acids in acidic, and un-ionized bases in basic environments." The rest can be extrapolated.

If the drug starts as **weak acid** (think "*it has a COOH group*"), then its **un-ionized state** is similar to COOH. It has that H^+ to give. If the drug gets into a solution with a higher pH, with less H^+, that weak acid is going to give the solution the H^+, and end up with COO^-. COO^- is ionized, water soluble, trapped in the compartment. If that same drug gets into a solution with a lower pH, with more H^+, that solution is going to give the H^+ to the compound, and make the compound like COOH. Un-ionized, lipid soluble, can move between compartments.

If the drug starts as a **weak base** (think "*it has an NH_3^+ group*"), then its **ionized state** is similar to NH_3^+. If this drug gets into a solution with a higher pH, with less H^+, then the solution is going to take a H^+ from the drug, making the drug like NH_2. NH_2 is un-ionized, lipid soluble, and freely moves between compartments. If that drug gets into a solution with a lower pH, with more H^+, that solution is going to give the H^+ to the compound, and make the compound like NH_3^+, ionized, water soluble, trapped in the compartment. If that drug gets into a solution with a lower pH, with more H^+, that solution is going to give the H^+ to the compound, and make the compound like NH_3^+. Figured, water soluble trapped in the compartment.

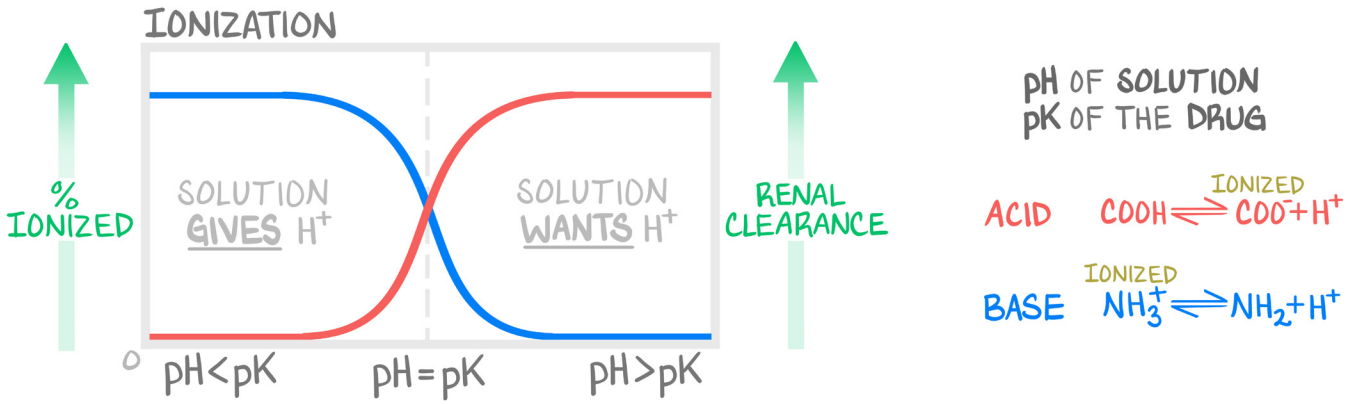

Figure 1.3: Graphical Representation of Ionization
This graph demonstrates how ionized a drug becomes relative to the pH of the solution. Because renal clearance of a drug is dependent on the drug's being hydrophilic (ionized), the more ionized a drug, the better the renal clearance, so the degree or percentage that a drug is ionized parallels renal clearance. Following the weak base, it is the most ionized in acidic environments, and is more ionized in the most acidic environments, but the least ionized in the most basic environments. The inverse is true of the red trace for a weak acid.

Why this matters, and why we've spent so much time on it, is because different environments have different pHs and different drugs have different p*K*s. The **stomach is acidic** and can change the absorption of a drug. **Proton pump inhibitors**, which reduce the acidity of the stomach, raising the pH, will alter a drug's absorption. Likewise, if we're trying to **trap a drug in the urine**, we'll want to make it ionized. If a drug **is a weak acid**, **raising the urine's pH** (alkalinization of the urine) will ionize the acid, and trap it in the urine for elimination. If the drug **is a base**, making the **urine's pH acidotic** (acidification) will ionize the base and trap it for elimination. Or if a tissue is inflamed (acidic), it'll change how anesthetics like lidocaine work. pH and p*K* matter.